NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

December 20, 1999

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Dear Sir/Madam:

Thank you very much for the opportunity to allow the National Hemophilia Foundation (NHF) to submit comments on the advanced notice of proposed rulemaking entitled "Plasma Derivatives and Other Blood-Derived Products; Requirements for Tracking and Notification." We are very pleased that the FDA has introduced this advanced notice and is considering possible regulation to further ensure that the end user of product will receive proper and expeditious notification of a recall or market withdrawal.

At the November 22, 1999 public hearing on this advanced rule the NHF stated that the FDA has both the authority and obligation to protect the public from unsafe or ineffective biological products. Thus the NHF once again promulgated the establishment of a two-tier system designed to assure both the swiftness and completeness of the notification process. The first tier of this system calls for regulation mandating that industry participate, through an independent third party, in direct notification of consumers who register for such notification. The second tier of this system would require the tracking of products from the manufacturer through consignees and ultimately to the patients and would require compliance by all parties within the custody chain. Pharmacies and other distributors would be required to maintain logs, including lot numbers of product; thus ensuring that tracking to the end user would be possible.

We are pleased that the FDA issued such a wide ranging advanced notice in which many questions are asked. The following are our responses to each of the several questions/request for comments posed in the ANPRM.

FDA invites comments and recommendations on how appropriate information regarding product safety can be provided to such patients (those who take custody of product for administration at home) and whether alternative procedures for such a system should be codified as part of the notification rulemaking.

The timely and effective dispersal of information about market withdrawals or recalls will require the establishment of a two-tier notification system. The fastest way for the patient to be informed is a mandatory system in which a manufacturer retains an independent third party to notify registrants. The third party can easily provide a variety of methods by which the consumer can choose to be notified (phone, fax, e-mail, and overnight letter). This

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should be mandated through regulation in order to codify the obligation of the manufacturer to notify its customers of an adverse event concerning a blood product and to assure the integrity of the system.

It must be recognized that not all patients will choose to sign up for a third party notification program. Reasons include discomfort with confidentiality issues, or dissuasion from registering by physicians or homecare companies who believe product notification falls within their own purview. However, regardless of reason, patients who are not enrolled in the third party system are no less entitled to notification of product recalls or withdrawals. Thus, establishment of a system in which notification follows the product is also required. This would entail tracking products from the manufacturer through consignees and ultimately to the patients and would require compliance by all parties within the chain of custody. Pharmacies and other distributors would be required to maintain logs, including lot numbers of product, to ensure that the end-user would be notified. Compliance must be mandatory and enforceable through regulation.

FDA also invites comments as to whether other blood products should be included (besides coagulation factor, alpha-1 protease inhibitors and IVIG) under the regulations, including a discussion of the extent of the increased burdens and public health advantages associated with such an expansion.

Recombinant analogs of coagulation factors are currently included in the voluntary Patient Notification System and the NHF strongly encourages that any prospective notification system also incorporate these products. Most of these recombinant products continue to use human and/or animal-derived proteins in their manufacture and albumin as a stabilizer. Additionally, there are many patients who use recombinant and plasma-derived products interchangeably. A notification regarding just one class of product would be both confusing and inefficient. Other pooled plasma products, such as solvent detergent-treated plasma (Plas+SD, Vitex) should also be subjected to notification, as should intramuscular immune globulin (IMIG).

FDA requests data on the effectiveness of such (current) systems in identifying all persons who may have custody of a plasma derivative product and notifying them in case the product is associated with a potential increased risk of transmitting a communicable disease.

The current, voluntary Patient Notification System operated by the National Notification Center, under contract with the International Plasma Products Industry Association (IPPIA), has been a great resource for individuals who have successfully enrolled. In this system, interested parties register with a designated third party that provides registrants with notices of product withdrawals or recalls by one of several rapid means of communication. Thus patients who often hold quantities of blood products in their homes, and their healthcare providers, can receive timely notification of defects in these products, thus preventing their

inadvertent use. NHF believes that industry has acted in a highly sensitive and responsible manner in establishing the Patient Notification System. For the most part, the system has functioned properly, although there have been anecdotal reports of difficulties encountered in both the registration and notification processes.

Unfortunately, enrollment to date in the Patient Notification System has been slow. Beyond the issue of patient accrual, there is concern that a company may unilaterally withdraw from this voluntary system. In fact, one company has already raised the possibility that it may do so. A mandatory system would ensure current participation and require several companies to join that do not yet participate.

Additionally, NHF is disappointed with the marketing effort for the Patient Notification System. It is time for IPPIA to take a step back and develop a comprehensive education and marketing program to ensure that the correct message is reaching potential enrollees. Undoubtedly they are many reasons for low enrollment; however, we have little but anecdotal information to understand this fact. Nevertheless, we do believe IPPIA must generate the support of treaters, hemophilia treatment centers, and homecare companies for the Patient Notification System and engage their active participation. Without the active support of all participants in the distribution process end-users are less inclined to enroll. NHF is ready and willing to assist in this effort as a part of an overall coordinated approach.

FDA also requests comments on whether such a system may be improved and, if so, whether regulations establishing a mandatory notification process would remain appropriate.

Information systems can always be improved and the NHF is fully prepared to join with industry and other consumer organizations to make the system better. However, only through regulation can continued industry participation be assured. Moreover, performance standards must be promulgated and adherence to those standards must be maintained through enforceable FDA regulation and oversight.

FDA is inviting comments on how the basis for notification should be defined in the regulations so as to appropriately establish the criteria for determining when notification should be required. FDA is also inviting comments and information on whether the scope should be expanded to cover other instances, which may affect the safety of product but which may not be associated with a potential increased risk of communicable disease.

In the advanced rule, the FDA states that they "intend the proposed regulations only for those plasma products associated with a potential risk or transmitting a communicable disease" and "that notification of end-users should take place in the same instance for which manufacturers are now recalling or withdrawing plasma derivative products because of a potential increased risk of transmitting disease." The irreducible potential of blood and blood-derived products to transmit infectious disease distinguishes these from most of the other products under FDA

regulatory jurisdiction. We propose that all recalls and withdrawals be subject to mandatory notification due to an increase in such risks.

We also believe that FDA has the authority and obligation to protect the public from unsafe or ineffective biological products irrespective of their infectious risk. Although the potential for such defects is not unique to plasma-derived products, we feel that since a notification system will be in place it would be both confusing to the intended recipient and an ineffective use of this resource not to include all notices of product withdrawal or recall.

FDA invites comments on the adequacy of the current recall process in situations, other than those related to the risk of communicable disease, and the additional benefits that would be provided by requiring patient notification when compared with the additional burdens associated with the notification process.

Given a fully operational notification system, the marginal costs associated with notification for product defects not related to infectious risk should be small and are far outweighed by the benefits.

FDA invites comments as to whether the consignees should be held responsible for notification, whether a manufacturer should be required to contract with a third party to perform notification, or whether either option should be permitted under the regulations.

NHF believes that for direct patient notification to be successful confidentiality must be assured and a manufacturer should therefore be required to contract with a third party entity. Notification of the end-user is the ultimate responsibility of the manufacturer. With that said, NHF also believes that to assure the effectiveness of the proposed second tier of the notification system, in which notification of a recall or withdrawal follows the product, consignees must also share in the responsibility. This would ideally be accomplished through regulated compliance by all parties within the chain of product custody.

FDA invites comments, data, and other information on the potential record keeping burdens that would be associated with tracking such plasma derivative products (plasma derivatives prescribed for home use), including any estimates of the time it would take to prepare such records and of the number of record keeping entries that would be necessary each year to maintain such records.

There are manufacturing industries, such as automobile and certain medical devices, which have tracking systems in place so that the product can be traced from production to the end user. We believe that such a system is entirely achievable for the blood products industry. Advances in information technology make tracking product through the chain of custody not only feasible, but also not unduly burdensome.

FDA request comments on what should be the required elements of the determination that mandatory notification is to take place and what information regarding that determination should be shared between the FDA and the manufacturer.

The requirements for mandatory notification should be the same as those for recall or market withdrawal of product. Although it could be argued that certain market withdrawals, such as for minor defects in product labeling, pose no more than a very minor threat to patient safety, differentiating among these would appear to be far more burdensome than simply issuing the notification through an existing system.

FDA invites comments and information on how rapidly it is feasible to attempt to contact patients who may possess the product subject to notification and how much time should be allotted to complete the notification process.

NHF would suggest 24 hours as a reasonable period of time in which direct patient notification should take place. This timeframe is concordant with that agreed upon by industry and consumer organizations in the current voluntary system. This goal has proved to be attainable and not overly burdensome. Notification of patients through the chain of custody is recognized as a far more time-consuming procedure that will depend on large part on the number of consignees involved. It is hoped that such a process would require not more than five to seven days.

FDA also invites comments on how much time should be permitted to contact consignees, other than patients with custody of the product, who also may be in possession of the product.

As in the case of direct patient notification, 24 hours would appear to be a reasonable period of time in which manufacturers can notify immediate consignees, perhaps using the same mechanisms as currently employed for notification of individuals.

FDA invites comments on the comparative advantages and disadvantages of notifying only those patients who may possess the product lot in question versus notifying all patients who may possess the indicated brand of plasma derivative.

It is envisioned that the direct notification component of the system would permit consumers and other interested parties to chose between these options. In the chain of custody component of the system, we advocate lot-specific notification of consignees and end-users.

FDA invites comments on whether the previous information (specific lot information, statement of risk, instructions for further action to be taken by patients who have custody of the product lot in question) is appropriate and adequately comprehensive for notification.

In addition to the aforementioned, NHF would also suggest including the reason for the recall or withdrawal.

FDA invites comments on the most appropriate means for evaluating the effectiveness of the notification process and who (the manufacturer, consignees, a third party) should be involved in such an evaluation.

The NHF proposes that representatives of all parties involved in the notification process (industry, consumer groups, other consignees) be invited to participate in an advisory committee, one of whose functions would be to regularly evaluate the effectiveness of the notification process. We believe, however, that notification should be governed by FDA regulation and that FDA should retain ultimate responsibility for the integrity of the system and compliance with its regulation.

FDA invites comments on the interrelationship among product recalls, withdrawals, and the notification process described in this ANPRM. What recall/withdrawal procedures would continue to be appropriate in the event FDA requires patient notification? How may the process best be integrated to ensure effective notification and product removal?

NHF believes that the existing recall/withdrawal process is sound and that notification should follow any FDA decision that recall/withdrawal actions are required.

FDA invites comments on whether such information (informing the patient that he or she will be notified if the product in custody is associated for a potentially increased risk) can best be provided in the form of patient labeling accompanying the product or should be delivered by other means. FDA also invites comments on whether such information can be standardized for all plasma derivative products and, if so, who should be responsible for preparing such information.

Information concerning notification should be included on either the label or in a package insert. Such labeling should invite participation in the direct notification process as well as inform the consumer that his/her direct supplier will be providing such information. This labeling can use language appropriate to all plasma-derived products and their recombinant analogs. The FDA would be ultimately responsible for approving such language, which may be supplied by individual manufacturers.

Once again, NHF is very appreciative of the opportunity to comment on this advanced notice of proposed rulemaking. Please feel free to contact us should you have any questions or would like to discuss our comments in more detail.

Sincerely,

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Executive Director & CEO

Bruce M. Ewenstein, M.D., Ph.D.
Co-Chair, Blood Safety Working Group

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